

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
SULFURYL FLUORIDE

Chemical Code # 000618, Tolerance # 50223
SB 950 # 498

August 1, 1986

Revised 2/27/87, 8/25/89, 9/17/90, 1/30/91, 4/10/92, 7/24/92, 9/14/94, 11/17/98,
4/23/02, and 6/2/04

I. DATA GAP STATUS

Chronic, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, possible adverse effect (not oncogenicity)
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time (see special studies)

Toxicology one-liners are attached.

In the one-liners below:

** indicates an acceptable study. **Bold face** indicates a possible adverse effect.

All relevant record numbers through 210013 (Document No. 50223-067) and all relevant records of the series 900000+ were examined. This includes all records listed in the DPR Data Index as of 6/2/04.

Updated by C. Aldous, 1/30/91; H. Green, C. Aldous, and J. Gee on 4/10/92; Gee, 7/24/92; and Kishiyama, Green, Kellner and Aldous, 9/14/94; C. Aldous, 11/17/98 and 4/23/02; P. Leung, 6/2/04

File name: T20040602.wpd

.

I. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED (CHRONIC and ONCOGENICITY), RAT

****50223-029 125637** "Sulfuryl Fluoride: 2-Year Inhalation Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats", (J. F. Quast, G. J. Bradley and K. D. Nitschke, The Dow Chemical Co., Toxicology Research Laboratory, Lab Project Study ID K-016399-040, 8/18/93). Sulfuryl fluoride, stated purity 99.8%, was administered via inhalation at concentrations of 0, 5, 20, or 80 ppm to 50 Fischer 344 rats/sex/group for 6 hours/day, 5 days/week (except holidays) for 24 months. Fifteen additional rats/sex/dose level were included for a 12-month neurotoxicity study (Record No. 130056). Formally, the NOEL = 5 ppm, based on "very slight" degree of dental fluorosis (statistically significant in males). Since the fluorosis is considered as a biomarker of exposure rather than as an adverse effect, a practical NOAEL is 20 ppm, based on a host of changes at 80 ppm. The primary target organ was kidney. An exacerbation of the normal process of chronic progressive glomerulonephropathy was the primary cause of premature deaths in both sexes at that dose, with mineralization in a variety of tissues as common secondary effects. High dose females had increased incidence of brain vacuolation in cerebral cortex and in thalamic and hypothalamic areas, limited to "very slight" degree. Possible direct responses of respiratory tissues would include aggregates of alveolar macrophages in lungs (already evident at 1 year interim sacrifice), and inflammation of larynx and trachea. Findings in this study had either not appeared or had not reached advanced degree until well beyond the first year of the study, consistent with the majority of effects being secondary to renal toxicity. **Acceptable, with "possible adverse effect"** (chronic renal disease). No oncogenicity was evident. Kishiyama and Aldous, 9/14/94.

50223-042 161152 U.S. EPA review of Record #125637, above. Recent reviews of 3 study types were included in this record. The review corresponding to the above record agreed with the 1994 DPR review above in acceptability status, and in the determination that no oncogenic effect was indicated. There are no fundamental differences in study interpretation between the DPR and U.S. EPA reviews, except that the U.S. EPA placed the NOEL at 20 ppm whereas the DPR review placed the NOEL at 5 ppm. The difference was based on the use of dental fluorosis as a determinant of the LOEL by DPR, which finding was not considered by either reviewer as a pivotal endpoint for chronic/oncogenicity outcomes. Aldous, 11/17/98.

CHRONIC TOXICITY, DOG

****50223-033 126744** "Sulfuryl Fluoride: One-Year Inhalation Toxicity Study in Beagle dogs", (J. F. Quast, M. J. Beekman, and K. D. Nitschke; Dow Chemical Company, Midland, MI; Report # K-016399-044; 21 October 1993). Sulfuryl fluoride, 99.8% purity. Four beagle dogs per sex per group were exposed via whole-body inhalation at 0, 20, 80, and 200 ppm for 6 hours per day, 5 days per week, for 1 year. High dose animals were killed at 9 months due to severe clinical signs of toxicity. NOEL = 20 ppm (very slight degree of chronic active inflammation in alveoli of the lungs of two 80 ppm females, multifocal aggregates of alveolar macrophages in both sexes, and very slight dental fluorosis). Alveolar inflammation was the main cause of rapid deterioration of health of most high dose dogs by about 9 months. A focal malacia in the caudate nucleus of the brain was identified in 5 high dose dogs, without apparent functional sequelae. **Acceptable. No adverse effects** are indicated, since subacute studies (see especially Record No. 097246) had already shown marked functional toxicity at 300 ppm, whereas about one-fourth of that daily dose in this chronic study caused only slight chronic effects. H. Green and C. Aldous, July 5, 1994.

50223-042 161152 U.S. EPA review of Record #126744, above. Recent reviews of 3 study types were included in this record. The review corresponding to the above record agreed with the 1994 DPR review above in acceptability status and NOEL. Aldous, 11/17/98.

50223-023 113430 Nitschke, K. D., Beekman, M. J., and Quast, J. F., "Sulfuryl fluoride: 13-week inhalation toxicity study in beagle dogs". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), 2/24/92. Four beagles/sex were dosed with SO₂F₂ by inhalation for 6 hr/day, 5 days/wk for 13 weeks. Doses were 0, 30, 100, and 200 ppm as whole body exposures in dynamic airflow chambers. High dose males and females gained less weight than other groups (final body weights of 200 ppm males and females were 12% and 4% lower than respective controls). The only clinical signs noted were one 200 ppm male with "lateral recumbency, tetany, tremors, salivation, and incoordination" noted on day 19 of the study only. Histopathology attributed to treatment was gliosis and vacuolation of focal areas of the putamen in one male and one female at 200 ppm. Microscopic changes are "possible adverse effects", however the presence of predictable clinical signs at the same dose level suggest that dose levels which do not elicit transient clinical signs are unlikely to cause marked histopathologic changes. The NOEL was 100 ppm. Results suggest that the chronic study should employ comparable dose levels to this subchronic study. Aldous, 4/1/92 (no separate worksheet).

50223-020 097246 Nitschke, K. D. and Quast, J. F., "Sulfuryl fluoride: Two-week inhalation toxicity study in beagle dogs". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), 4/30/91. Beagles, 1/sex, were dosed with nine 6-hr inhalation treatments of sulfuranyl fluoride (SO₂F₂) over two weeks. Concentrations were 0, 30, 100, or 300 ppm. The major clinical observation was intermittent tremors and tetany in both 300 ppm dogs from day 5 onward. The effects were severe enough on day 9 that exposure was terminated after 5.5 hr. Dogs rapidly recovered to normal appearance and behavior at the end of each exposure period. Nasal turbinates of 300 ppm dogs had a slightly greater degree of inflammation than background level, and a similar slight inflammatory response in mucosa of the trachea was noted in the 300 ppm female. The NOEL was 100 ppm. No separate DPR written review is needed for this study. Aldous, 4/1/91.

ONCOGENICITY, RAT
(see combined, rat, above)

ONCOGENICITY, MOUSE

****50223-028 125636** "Sulfuryl Fluoride: 18-Month Inhalation Oncogenicity Study in CD-1 Mice", (J. F. Quast, G. J. Bradley and K. D. Nitschke, Dow Chemical Co., Toxicology Research Laboratory, Lab Project Study ID K-016399-039, 8/19/93). Sulfuryl fluoride, 99.8% purity, was administered via inhalation at concentrations of 0, 5, 20, or 80 ppm to 50 CD-1 mice/sex/group for 6 hours/day, 5 days/week for 18 months. Ten additional mice/sex per dose level were included for sacrifice at 12 months. NOEL = 20 ppm. Primary concern was increased mortality in females (mainly due to increased incidence of severe degree of bilateral amyloidosis in glomeruli). Possibly treatment-related findings in males were food impaction in esophagus and inflammation and/or abscesses in the head and/or oral cavity at 80 ppm. Lesser changes at 80 ppm included very slight vacuolation of brain, particularly of cerebral external capsule (M and F), and very slight hypertrophy of thyroid epithelial cells (especially in males). This study is considered to indicate a "**possible adverse effect**", based on the exacerbation of geriatric renal disease in high dose females. Considering how high the NOEL and LOEL of this study are to levels which cannot be tolerated in acute and subacute toxicity exposure, this flagging of a "possible adverse effect" should not be taken to indicate unusual concern. No oncogenicity effects. **Acceptable.** Kishiyama and Aldous, Sept. 14, 1994.

50223-042 161152 U.S. EPA review of Record #125636, above. Recent reviews of 3 study types were included in this record. The review corresponding to the above record agreed with the 1994 DPR review above in acceptability status, NOEL, and in the determination that no oncogenic effect was indicated. Aldous, 11/17/98.

REPRODUCTION, RAT

**50223-022 112308 Breslin, W. J., Liberacki, A.B., Kirk, H. D., Bradley, G. J., and Crissman, J. W. "Sulfuryl fluoride: Two-generation inhalation reproduction study in Sprague-Dawley rats". The Toxicology Research Laboratory, Health and Environmental Sciences, Dow (Midland), Jan. 7, 1992. Sprague-Dawley rats were dosed 6 hr/day, 5 days/wk with sulfuryl fluoride at doses of 0, 5, 20, or 150 ppm. Thirty rats/sex/group were dosed for 10 wk or 12 wk prior to mating (F0 and F1 parents, respectively): dosing was continued to end of weaning period for both sexes, except that females were taken off treatment for 5 days beginning shortly before expected parturition. Pups were not exposed to sulfuryl fluoride prior to weaning. Parental NOEL = 5 ppm (aggregates of alveolar macrophages in lungs of both sexes, both generations: dose related). At 150 ppm, adults of both generations had body weight decrements of about 10% (generally statistically significant). This group had discolored teeth (fluorosis), chronic inflammation of lungs, and "very slight" to "slight" vacuolation of myelinated fiber tracts of the caudate putamen. Reproductive effects NOEL = 20 ppm (reduced pup body weights in F1 and F2 generations). Study is ACCEPTABLE. No adverse reproductive effects. The comparatively low NOEL for systemic effects may nevertheless be useful in eventual risk assessment. Aldous, 4/8/92.

50223-018 095931 Draft protocol for 50223-022 112308, above.

TERATOLOGY, RAT

**006 36089 Rat Teratology, 833. (Toxicology Research Laboratory, Dow Chemical, 10/26/81). "Vikane: Inhalation teratology study in rats and rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity) at 0, 25, 75, or 225 ppm by inhalation for 6 hours/day on days 6 through 15 of gestation. Dose levels based on a probe study. Maternal and developmental NOEL's > 225 ppm (HDT). J. Parker evaluation (7/24/86) found study unacceptable but possibly upgradeable; B. Davis evaluation (2/6/87) was complete and ACCEPTABLE with supplemental data (007:051087).

007 051087 Data supplemental to a rat teratology study 006:036089, above. (Toxicology Research Laboratory, Dow Chemical, 11/19/80). "Vikane: Probe teratology study in Fischer 344 rats and New Zealand white rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity). Results from a range-finding study show decreases in maternal body weight, body weight gain, and food consumption, and increases in water consumption and kidney weights at the 300 ppm exposure level, with no toxicity at 100, 30, or 0 ppm. Summary and individual antemortem observations, individual necropsy data, and individual litter and fetal data are provided. This supplement removes all deficiencies and the teratology is complete and acceptable. B. Davis 2/6/87.

TERATOLOGY, RABBIT

**006 36088 (Toxicology Research Laboratory, Dow Chemical, 10/26/81). Rabbit teratology (833). "Vikane: Inhalation teratology study in rats and rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity) at 0, 25, 75, or 225 ppm by inhalation for 6 hours/day on days 6 through 18 of gestation. Maternal (decreased weight gain) and developmental (decreased fetal weight) NOEL's = 75 ppm. J. Parker evaluation (7/24/86) found study unacceptable but upgradeable; B. Davis evaluation (2/6/87) was complete and ACCEPTABLE with supplemental data (007 050992).

007 050992 Data supplemental to a rabbit teratology study in 006:036088. (Toxicology Research Laboratory, Dow Chemical, 11/19/80). "Vikane: Probe teratology study in Fischer 344 rats and New Zealand white rabbits." Vikane = sulfuryl fluoride = SO_2F_2 (99.8% purity). Results from a range-finding study show decreases in maternal body weight, body weight gain, and liver weights at the 300 ppm exposure level, with similar but not statistically significant toxicity at 100 ppm. Summary and individual antemortem observations, individual necropsy data, and individual litter and fetal data are provided. This supplement removes all deficiencies of the teratology study. B. Davis 2/6/87.

GENE MUTATION

** 016 091291 "Evaluation of Sulfuryl Fluoride in the Ames Salmonella/Mammalian-Microsome Bacterial Mutagenicity Assay." (Gollapudi, B. B., Samson, Y. E. and Zempel, J. A.; Health and Environmental Sciences-Texas, Dow, TXT:K-016399-037, 8/17/90). Sulfuryl fluoride gas, lot 874, 99.6%, was tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 with and without activation with rat liver S9. Overnight cultures were plated in top agar, then exposed without lids for 4 hours in glass desiccators. Atmospheres of 0, 300, 1000, 3000, 10,000 and 30,000 ppm were tested. After exposure, plates were incubated an additional 2 days, then the colonies were counted. Triplicate plates per concentration and two trials were studied. There was no evidence of an increase in reversion rate. The number of revertants was decreased somewhat at 30,000 ppm suggesting cytotoxicity. The positive controls were acceptable. ACCEPTABLE. (Gee, 9/14/90).

CHROMOSOME EFFECTS

**014, 017 090476, 091576 "Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test" (Gollapudi, B. B., McClintock, M. L. and Nitschke, K. D., Toxicology Research Laboratory, Dow, Project ID: TXT:K-016399-033, 2/16/90). Sulfuryl fluoride, Lot WP880329 752 MAR/88, 99.6%, was administered to CD-1 mice in an inhalation chamber for a 4 hour exposure period. Actual concentrations of sulfuryl fluoride were 0, 48, 180 and 520 ppm, TWA. Benzene was a positive control with a target concentration of 9000 ppm. Cyclophosphamide was an additional positive control at 120 mg/kg by gavage. The positive controls were sampled 24 hours after exposure, the negative control and treated animals were sampled 24, 48 or 72 hours after exposure, 5/sex/group for each time point. 1000 PCE/animal were evaluated and the percent PCE determined. No increase in the number of micronucleated cells. ACCEPTABLE. (D. Shimer and J. Gee, 9/14/90).

025 115686 "Response to U. S. EPA Comments on the Study Entitled 'Evaluation of Sulfuryl Fluoride in the Mouse Bone Marrow Micronucleus Test' Laboratory Project ID: TXT:K-016399-033" (K. D. Nitschke and B. B. Gollapudi, DowElanco, 1991) The U. S. EPA rejected the study as unacceptable based on the following: 1) No evidence for an MTD and 2) several parameters of exposure were not provided, namely, identity of the inhalation chamber, use of Miran-1A infrared spectrophotometry, no location for sampling devices or placement of animals in the chamber. The submission contains DowElanco's response. The study was ACCEPTABLE to DPR. No change in status. No worksheet. Gee, 7/24/92.

DNA DAMAGE

** 50223-021 093262, "Evaluation of Sulfuryl Fluoride in the Rat Hepatocyte Unscheduled DNA Synthesis (UDS) Assay", (B. Bhaskar Gollapudi, et al., Health and Environmental Sciences-Texas, The Dow Chemical Co., Report # K-016399-043, 10/7/91). Sulfuryl fluoride (gas fumigant), 97.4% purity, was tested in the unscheduled DNA synthesis assay using hepatocytes of

Sprague-Dawley outbred Crl:CD BR male rats at concentrations of 0 (air), 204, 408, 612, 816, 1020, or 1530 ppm. No increase in unscheduled DNA synthesis by autoradiography. ACCEPTABLE. (H. Green and J. Gee, 4/10/92)

NEUROTOXICITY

Acute hen studies are not routinely required for this class of chemicals. Nevertheless, several specialized studies have been done, as follows.

****50223-035 130056** "Sulfuryl Fluoride: Chronic Neurotoxicity Study in Fischer 344 Rats-Final Report" (P. J. Spencer, G. J. Bradley and J. F. Quast, Dow Chemical Co., Toxicology Research Laboratory, Lab. Project ID K-016399-040B 3/24/94). Sulfuryl fluoride (purity 99.8%, lots WP 880329-752, WP 901011-907, WP 910321-918, WP 910826-929 and WP 920131-940) was administered via whole-body inhalation (6 hours/day, 5 days/week) for 1 year at concentrations of 0, 5, 20 or 80 ppm to 15 Fischer 344 rats/sex/group (satellite rats from concurrent 2-year chronic toxicity/oncogenicity study). NOEL (for neurotoxicity) = 80 ppm. **No Adverse Effects.** Functional observational battery, grip performance, landing foot splay and motor activity tests showed no evidence of neurotoxicity. ACCEPTABLE. Supplemental information. Kellner, Aldous and Gee, 9/14/94.

50223-031 126406 Exact duplicate of Appendix IV of Record No. 130056.

50223-010 071482 Mattsson, J. L., Albee, R. R., Eisenbrandt, D. L., and Nitschke, K. D. "Neurological examination of Fischer 344 rats exposed to sulfuryl fluoride (Vikane™ gas fumigant) for 13 weeks". (Mammalian and Environmental Toxicology Research Laboratory, Dow, study ID K-016399-026, 11/21/86). Vikane, Lot TWP 830919-408, 99.8%, was administered to Fischer 344 rats, 7/sex/group, 6 hours/day, 5 days/week, for 13 weeks at 0, 30, 100 or 300 ppm. Rats were implanted with epidural electrodes, and a battery of neurological tests was performed on the rats after 13 weeks of exposure. At 300 ppm, rats had increased latencies of certain components of various evoked response wave patterns (visual, somatosensory, cerebellar, auditory). In addition, visual and somatosensory evoked responses were noted as statistically significantly slowed in females at 100 ppm, and the latency of the auditory brainstem response in 100 ppm males appeared to be increased. Thus the NOEL was 30 ppm. The only brain microscopic findings at the end of the treatment period were vacuoles in the white fiber tracts of the caudate-putamen. Auditory brainstem response was tested in controls and high dose rats (2/dose/sex) after 2 months of recovery, at which time rats were sacrificed and brains were examined microscopically. After recovery, 300 ppm rats had normal evoked responses and normal brain histology. Brain functional changes are **possible adverse effects. Useful supplemental data.** D. Shimer/ C. Aldous, 9/13/90.

009 071478 "Subchronic Neurotoxicity in Rats of the Structural Fumigant, Sulfuryl Fluoride" (Health and Environmental Sciences, Dow Chemical Co., Mattsson, J. L., R. R. Albee, D. L. Eisenbrandt and L. W. Chang, Neurotoxicol. Teratol. 10(2) 127-133. 1988., 3/11/87). This is the published version of study 50223-010:071482 (see above).

50223-030 126302 "Sulfuryl Fluoride: Electrodiagnostic, FOB and Motor Activity Evaluation of Nervous System Effects from Short-Term Exposure", (R. R. Albee, P. J. Spencer, and G. J. Bradley, Dow Chemical Co., Toxicology Research Laboratory, Lab. Project ID K-016399-045, K-016399-045D, K-016399-045E, K-016399-045F, and K-016399-045G, 5/3/93). This study was requested by U.S. EPA to achieve limited objectives as indicated in the title. Previous studies had addressed histopathology and other features commonly included in neurotoxicity studies. Sulfuryl fluoride, purity 98.3-99.8%, was administered via whole-body inhalation (6 hours/day for 2 consecutive days) at concentrations of 0, 100 or 300 ppm to 12 non-pregnant female Fischer rats/group. NOEL = 300 ppm. Functional observational battery, grip performance, landing foot

splay, motor activity and electrodiagnostic responses were examined within 24 hr of the final exposure. There was no evidence of neurotoxicity. Not applicable to fill guideline FIFRA study data gaps, but useful information. (Kishiyama and Aldous, 9/7/94).

SUBCHRONIC, INHALATION

****50223-012 071484** Nitschke, K. D., Zimmer, M.A., and Eisenbrandt, D. L. "Sulfuryl Fluoride (Vikane™ Gas Fumigant): 13-Week Inhalation Toxicity Study with Rabbits" (Mammalian and Environmental Toxicology Research Laboratory, Dow Chemical Company, Study ID K-016399-025B, 11/16/87). Vikane, sulfuryl fluoride, Lot No. TWP 830919-408, 99.8%, was administered to New Zealand White rabbits via inhalation for 6 hours/day, 5 days/week for 13 weeks at 0, 30, 100 or 300 ppm. Seven animals per sex per group. NOEL = 30 ppm; [cerebral vacuolation in regions of internal and external capsules, putamen, and globus pallidus of one female: and nasal tissue inflammation in one male]. At 300 ppm, common brain findings were vacuolation to severe malacia of cerebrum (both sexes, in the above regions), and gliosis and/or hypertrophy of vascular endothelial cells in some females in the same regions. Common nasal tissue findings at 300 ppm in both sexes were degeneration and inflammation of epithelial tissues. Collectively, these findings are **possible adverse effects. Acceptable subchronic study.** D. Shimer/ C. Aldous, 9/10/90.

****50223-012 071485** Nitschke, K. D., Dittenber, D.A., and Eisenbrandt, D. L. "Sulfuryl Fluoride (Vikane Gas Fumigant): 13-Week Inhalation Toxicity Study with Rats" (Mammalian and Environmental Toxicology Research Laboratory, Dow Chem. Co., Project ID K-016399-025R, 11/16/87). Vikane, sulfuryl fluoride, Lot TWP 830919-408, 99.8%, was administered by inhalation to Fischer 344 rats, 10/sex/group, at 0, 30, 100 or 300 ppm for 6 hours/day, 5 days/week, 13 weeks. NOEL = 30 ppm (based on mottled incisors in all rats at 100 and 300 ppm). A practical NOAEL relevant to adults likely to be exposed chronically is 100 ppm. Major findings at 300 ppm included: marked body weight decrements (M & F), cerebral vacuolation [caudate-putamen area, white fiber tracts of the internal capsule; (M and F)], kidney hyperplasia (F) and decreased protein droplets in kidneys (M), inflammation of nasal mucosae (M & F), and subpleural histiocytosis in the lungs (M & F). Brain findings constitute **possible adverse effects. Acceptable** as a subchronic study. Shimer/Aldous; 9/17/90.

50223-018 095933 Exact duplicate of record No. 071485, above.

50223-018 095932 Eisenbrandt, D. L., Nitschke, K. D., Streeter, C.M., Wolfe, E. L. "Sulfuryl fluoride (Vikane® Gas Fumigant): 2-Week inhalation toxicity probe with rats and rabbits". Dow Chemical Co., Midland MI, April 2, 1985. Dose levels were 0, 100, 300, or 600 ppm in both species. Animals were exposed for 6 hr/day for a total of 9 days. Nine out of 10 rats administered 600 ppm sulfuryl fluoride died. Kidneys of these rats were severely affected. Minor kidney damage was noted in 300 ppm rats. There were no other apparent effects at that dose level. Reviewed by Aldous, 1/30/91 in the context of a protocol review for a reproduction study scheduled to begin in Feb., 1991. (See CDFA protocol comments of 1/30/91).

50223-034 128669 "DowElanco sulfuryl fluoride: Thirteen-week inhalation study in CD-1 mice" (329 pages). Source Lab: The Dow Chemical Company, Midland, MI. Study Date: 12/93. Study was not reviewed by DPR, but an abstract was included in the oncogenicity study for which this study served as a dose range-finding study (see review of Record No.125636). Aldous, 11/17/98.

****50223-055 186125** Nitschke, K. D. and J. F. Quast, "Sulfuryl fluoride: two-week inhalation toxicity study in CD-1 mice," The Dow Chemical Co., Midland, MI, 2/11/02. Laboratory Project Study # K-016399-029. Five mice/sex/group were dosed 6 hr/day, 5 days/wk, for 9 exposures at 0, 30, 100, and 300 ppm sulfuryl fluoride, 99.6% purity. Associated exposures of treated groups were 0.13, 0.42, and 1.3 mg/l of chamber air. Mice were sacrificed 1 day after the last exposure,

at which time they were subjected to limited hematology and clinical chemistry studies, gross necropsy and histopathology. NOEL = 30 ppm ("very slight" cerebral vacuolation in six of ten 100 ppm mice). The 300 ppm exposure proved to be excessive: 9/10 of these mice did not survive the 11-day duration of the study. Deaths were preceded by inanition (statistically significantly body weight losses, decreased ingesta in digestive tract, decreased body fat), and associated pathology (stomach erosions/ulcers, hepatocellular atrophy judged to be due to inanition). Most decedents had "roughened hair coat" and at least 3 of the males had whole body tremors. All high dose mice, except for 2 with sufficient autolysis to impede microscopic evaluation, showed cerebral vacuolation, usually of "moderate" degree. Five high dose mice had very slight vacuolation of the medulla. These brain lesions are "**possible adverse effects.**" Also, nine high dose mice had lacrimal/Harderian gland atrophy. **Acceptable.** Aldous, 4/23/02.

50223-036 131289 (2 pages of additional information related to 50223-034 128669, above).

SPECIAL STUDIES

009 071479 "Incapacitation and Treatment of Rats Exposed to a Lethal Dose of Sulfuryl Fluoride" (Health and Environmental Sciences, Dow Chem. Co., Nitschke, K. D., Albee, R. R., Mattsson, J. L. and Miller, R. R. (1986) Fundam. Appl. Toxicol. 7, 664-670. Sulfuryl fluoride, 99.8% was administered to Fischer 344 rats in exercise chamber at 400, 10,000, 20,000 or 40,000 ppm to determine "time to incapacitation" and to see if calcium gluconate (treatment for fluoride ion toxicity) would alleviate effects of a lethal dose. Rats exposed to 4000 ppm for 45 minutes could walk for 45 minutes, then died about 2.5 hours after exposure terminated. Four out of five rats treated with calcium gluconate prior to exposure survived at least 3 days. Three anticonvulsants: diphenylhydantoin, phenobarbital, and diazepam, were given to some groups prior to treatment. Phenobarbital was effective in controlling convulsions. Potentially useful supplemental information, however not relevant to SB-950 data review at this time. No DPR worksheet has been done, nor is one anticipated at present. D. Shimer, 8/25/89. (Comments by Aldous, 9/17/90: no toxicologist review).

METABOLISM

****50223-0067 210013, "Sulfuryl Fluoride: Pharmacokinetics and Metabolism in Fischer 344 Rats", (A. L. Mendrala, *et.al.*, Toxicology & Environmental Research and Consulting, The Dow Chemical Company, Midland, MI, Study ID 001166, 22 May 2002).** 4 jugular vein cannulated Fischer 344 male rats and 4 non-cannulated males per group received nose-only inhalation exposure (4 hours) to ³⁵S-Sulfuryl Fluoride at 30 and 300 ppm. Additionally, 18 non-cannulated males per group were exposed (4 hours, nose-only inhalation) to non-radiolabelled sulfuryl fluoride at 30 and 300 ppm and 8 non-cannulated males served as a vehicle control (dry, compressed air) group. Time-weighted actual exposure concentrations over the 4-hour treatment period with ³⁵S-sulfuryl fluoride were 28.4 ppm (0.26 μ Ci/l of atmosphere) and 274 ppm (2.8 μ Ci/l of atmosphere) at the 30 ppm and 300 ppm nominal levels respectively. Values were 31.2 ppm and 312 ppm at 30 ppm and 300 ppm respectively for non-radiolabelled sulfuryl fluoride exposures. Venous blood samples (~0.15 ml) were collected from cannulated rats at 0.25, 0.5, 1, 2, 3, and 4 hours during inhalation exposure and 0.5, 1, 2, 4, 6, 12, 24, 36, 48, 72, 96, 120, and 168 hours post-exposure. 3 animals per group exposed to non-radiolabelled sulfuryl fluoride were sacrificed after 2 and 4 hours of exposure and 2, 4, 8, and 20 hours post-exposure to measure fluoride ion content in plasma, brain, and kidney. Additionally, fluoride ion content was determined in plasma, brain, and kidney of 2 control rats per group at the beginning and end of exposure and 4 and 8 hours post-exposure. No radioactivity was detected in expired air of the 300 ppm group animals at 24 hours post-exposure, therefore, collection of expired air was not continued for the remaining sampling intervals of the group and not performed at all for 30 ppm animals. Plasma and RBC Radioactivity after ³⁵S-Sulfuryl Fluoride Exposure. Plasma levels of

radioactivity peaked at 5.2 and 37.7 $\mu\text{g-eq./g}$ ($\mu\text{g-eq./g}$) at 30 and 300 ppm respectively at the end of exposure. From the end of exposure to 24 hours post-exposure (α phase), half-lives were 2.6 and 2.4 hours at 30 and 300 ppm respectively, and from 24 hours post-exposure on (β phase), half-lives were 82.7 and 56.2 respectively. RBC radioactivity reached 4.7 and 40.3 $\mu\text{g-eq./g}$ RBC at 30 and 300 ppm respectively at the end of exposure. α phase half lives were 2.5 and 1.1 hours and β phase half-lives were 222 and 139 hours at 30 and 300 ppm respectively.

Urinary and Fecal Excretion after ^{35}S -Sulfuryl Fluoride Exposure. Urine contained 85.6% to 88.9% of excreted radioactivity through 7 days post-exposure (580.636 and 4618.051 $\mu\text{g-eq}$ at 30 and 300 ppm respectively). 47% (273 $\mu\text{g-eq.}$) and 60% (2766 $\mu\text{g-eq}$) were excreted during the 4 hour exposure period at 30 and 300 ppm respectively. 73 and 777 $\mu\text{g-eq.}$ of radioactivity were recovered in feces through 7 days post-exposure at 30 and 300 ppm respectively. 70 and 704 $\mu\text{g-eq.}$ respectively were recovered through 48 hours post-exposure.

Tissue Distribution after ^{35}S -Sulfuryl Fluoride Exposure. The lungs had the highest concentration of radioactivity, 0.77 and 6.30 $\mu\text{g-eq./g}$ at 30 and 300 ppm respectively 7 days post-exposure. Respiratory turbinates contained 0.312 and 3.491 $\mu\text{g-eq./g}$, olfactory turbinates - 0.285 and 3.233 $\mu\text{g-eq./g}$, spleen - 0.394 and 3.075 $\mu\text{g-eq./g}$, and kidneys - 0.368 and 2.756 $\mu\text{g-eq./g}$ at 30 and 300 ppm respectively.

Metabolites Identified Following ^{35}S -Sulfuryl Fluoride Exposure. Two radiolabelled metabolites, sulfate and fluorosulfate, both hydrolysis products of sulfuryl fluoride, were identified in whole blood and urine.

Fluoride Ion Analysis Following Non-Radiolabelled Sulfuryl Fluoride Exposure. Metabolic release of fluoride ions was proposed as the cause of toxicity in sulfuryl fluoride exposure (Nitschke, *et. al.* (1986), and Nitschke and Eisenbrandt (2001)), therefore, quantification was performed. Elevated levels of fluoride ion were detected in urine, plasma, kidney, and brain during and after exposure to non-radiolabelled sulfuryl fluoride. Most returned to background levels at varying times post-exposure. Acceptable. (Green and Gee, 6/1/04).